

Effectiveness of fixed-dose combination therapy in hypertension: systematic review and meta-analysis

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Abstract

Introduction: Clinical studies have revealed that fixed-dose combinations (FDCs) of drugs can have a better effect on blood pressure than free-equivalent combinations (FECs). Our objectives were to perform an up-to-date assessment of the effectiveness of FDCs and FECs in antihypertensive therapy, to provide more accurate results by using a stratified meta-analysis.

Material and methods: A systematic review was performed in PubMed, Web of Science, and Cochrane databases according to PRISMA guidelines. The outcomes were adherence (compliance), persistence to medication, reduction of blood pressure and the safety profile. We used the Newcastle Ottawa scale or the Delphi list for the assessment of the quality of cohort studies or clinical trials, respectively. Heterogeneity was assessed using the Cochrane *Q* test and *I*² statistic.

Results: Of 301 abstracts screened, 26 primary studies and 2 other meta-analyses were identified, of which 12 studies were included in the meta-analyses and 3 studies were included in the narrative review. The FDC treatment is associated with a significant improvement in adherence and persistence in comparison with FEC treatment, e.g., the average medicine possession ratio increased with FDC by 13.1% ($p < 0.001$). For endpoints correlated with higher adherence (e.g., a reduction in blood pressure), a non-significant benefit was observed for FDCs. Moreover, it was demonstrated that higher adherence can lead to a lower risk of cardiovascular events.

Conclusions: In comparison with FECs, the FDC treatment is associated with a significant improvement in the cooperation between a doctor and a patient and with increased patients' adherence to the treatment schedule.

Key words: fixed-dose combinations, free-equivalent combinations, hypertension.

Introduction

Hypertension is a common condition associated with substantial morbidity and mortality. Nowadays, over 1 billion people suffer from high blood pressure worldwide [1], and it is estimated that the prevalence of hypertension will have risen by an additional 27 million people by the year 2030 [2]. Improper management of hypertension can lead to cardiac failure, stroke, end-stage renal disease, and, finally, to death [3, 4]. Although blood pressure lowering is crucial in hypertension, about half

of the patients still have uncontrolled blood pressure [5].

The initial approach to blood pressure lowering is based on monotherapy, but in many cases, combination therapy is necessary to achieve target blood pressure levels [6]. Studies that assessed the difference in efficacy between monotherapy and polytherapy for blood pressure control have shown that combination therapy is more effective than monotherapy [7, 8]. Combination therapy is available either as a fixed-dose combination (FDC), which includes at least 2 active agents combined in a single pill (also known as a single-pill combination), or as a free-equivalent combination (FEC, also known as a free combination), which involves separate use of the corresponding drug components. Although the FEC is chemically equivalent to the FDC, a number of studies have indicated that the FDC can have a better impact on blood pressure control as well as reducing the use of medical resources by increasing patients' adherence (compliance) and persistence to treatment [9–12].

Systematic reviews published in 2010 and 2011 confirmed a significantly higher adherence rate among patients treated with an FDC compared with an FEC [12, 13], although without a significant impact on blood pressure levels [13]. It is noteworthy that previous reviews [12, 13] provide different conclusions regarding persistence.

We performed a systematic review and meta-analysis to provide an up-to-date evaluation of the effectiveness of FDCs in comparison with FECs in patients with hypertension to deliver precise effect sizes calculated throughout separate meta-analyses stratified according to the definition of outcomes related to: adherence, average medicine possession ratio (MPR) or average proportion of days covered (PDC) or probability of being adherent to treatment (i.e. with MPR or PDC $\geq 80\%$) or stratified according to the period of observation in case of persistence, incorporating generally accepted methodological standards (no synthesis of: prospective and retrospective studies, adjusted and unadjusted outcomes, or treating the rate of being adherent and the adherence rate as the same variable. Moreover, we aimed to provide systematically obtained evidence regarding effectiveness of FDCs in reducing rates of cardiovascular events.

We finally aimed to solve the problem of conflicting conclusions from previous reviews [12, 13] regarding higher persistence on FDC treatment in comparison with FEC treatment.

Material and methods

Search strategy and eligibility criteria

A systematic search of the literature was conducted in PubMed, Web of Science, and Cochrane

Controlled Trial Registry. No date restriction was applied to the search and the last search was performed on 14 April 2015. Comprehensive combinations of MeSH and free-text terms were used for the literature search to identify studies regarding hypertension, antihypertensive agents, and FDCs. The terms were then combined with the terms for the outcome of interest, including at least compliance, adherence, persistence, and adverse effects. The search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic literature reviews and meta-analyses [14]. Potentially relevant full-text publications were then screened for inclusion against the following predetermined criteria: patients with hypertension (population); fixed-dose combinations with or without additional drugs (intervention) compared with free-equivalent combinations with or without additional drugs (comparison); medication compliance/adherence, persistence, adverse events, systolic and diastolic arterial blood pressures, and safety of treatment as outcomes. No restrictions were applied as to the study design. The study was excluded if it did not comply with at least one inclusion criterion.

Within the framework of our systematic review, apart from primary research publications identified during the database search, we also took into consideration publications and conclusions presented in previously published systematic reviews [12, 13].

Records selected for retrieval were assessed by 2 independent reviewers for methodological validity before inclusion in the review using standardized critical appraisal instruments. Any disagreements were resolved through discussion or with the third independent reviewer.

Quality assessment of the included studies was done using either the Newcastle-Ottawa scale (cohort studies) [15] or the Delphi list (clinical trials) [16], and the studies were accordingly categorized into the following 4 categories: poor, fair, good, and excellent.

Data collection and synthesis

Quantitative data were extracted from papers included in the review using the standardized data extraction tables. The extracted data included specific details about the interventions, patients' characteristics, study design, methods of outcome analysis, and results of significance to the review questions and specific objectives. Data extraction and meta-analysis were conducted independently on the basis of all the identified studies providing an update and verification of the systematic reviews [12, 13].

Medication adherence (compliance) was defined according to: i) the number of the administered tablets as a medicine possession ratio (MPR)

estimated on the basis of the number of days of medication supply within the prescription refill interval [17–26] or ii) the percentage of days during which a medication was taken by patients, on the basis of the proportion of days covered (PDC) [27, 28]. A compliant (adherent) patient was defined as a patient with an MPR or PDC of 80% or higher. Persistence was described on the basis of the prescription refill interval as previously described by Gupta *et al.* [13].

We investigated the average estimate of adherence estimators (PDC or MPR), probability of being adherent to the prescribed treatment (MPR or PDC $\geq 80\%$), effectiveness in blood pressure lowering, as well as persistence rates and the rates of adverse events and cardiovascular events among all patients treated with an FDC or FEC. The publication bias was assessed by funnel plots and by Egger's or Begg's test. Effect sizes were expressed as odds ratios (ORs) for dichotomous data and weighted mean differences for continuous data. The 95% confidence intervals (CIs) were calculated for all measures. The results for time-to-event data were presented as a hazard ratio (if available) or as the average or median length of treatment calculated with nonparametric or semiparametric approaches (Kaplan-Meier or Cox model).

Standard methods were used for meta-analysis (Mantel-Haenszel fixed effect model and DerSimonian and Laird random effect model). Heterogeneity was assessed using the standard χ^2 (Cochrane Q) test and I^2 statistic. The random effects model was applied if significant heterogeneity between studies was revealed (a p -value of less than 0.1). Heterogeneity between studies was explored using subgroup analyses based on different quantitative study designs included in this review (prospective vs. retrospective), different measure of adherence (MPR vs. PDC), and different follow-up periods for dichotomous outcomes. The meta-regression for outcomes reported in more than 5 studies was also planned as an attempt to explain the heterogeneity. Where statistical pooling was not possible, the findings were presented in a narrative form including tables to enhance data presentation where appropriate.

All calculations were performed using the software R version 3.03 (R Core Team, 2014) and Excel 2013 (Microsoft). The 'metafor' package was used within the R environment [29].

Results

The electronic searches yielded 301 unique records after duplicates had been removed. The selection of titles and abstracts resulted in 34 potentially relevant articles (32 primary research studies and 2 systematic reviews), of which 6 articles were excluded (lack of appropriate data to

use, 1; analysis of other endpoints, 2; inadequate comparison, 3). The flow of information through the different phases of the systematic review is shown in Figure 1.

In a systematic review by Gupta *et al.* [13], conducted in 2010, 15 studies were taken into account: 5 randomized studies [17, 30–33] (1 parallel trial and 4 crossover trials, 2 double-blinded and 3 open trials), 4 nonrandomized crossover trials [18, 34–36], and 6 retrospective cohort studies [19–21, 37, 38] (a study by Dezii, 2000, presented data for 2 different treatment schedules, FDC vs. FEC; therefore, it was introduced separately).

In a systematic review by Sherrill *et al.* [12], 15 studies were taken into account: 1 randomized crossover multicenter study [17], 1 nonrandomized crossover multicenter study [18], and 13 retrospective cohort studies [19–26, 37, 39–42].

Six studies [17–21, 37] included in the review by Sherrill *et al.* [12] were also investigated by Gupta *et al.* [13]. Two studies (Malesker and Hilleman, 2010 [42], and Barron *et al.*, 2008 [41]), which were included by Sherrill *et al.* [12], were excluded from our analysis because they focused on the analysis of other endpoints. Two bibliographic records [22, 23] identified by Sherrill *et al.* [12] were related to the studies included by Gupta *et al.* [13].

In our analysis a conference abstract (Jackson *et al.*, 2006 [38]) included in the review by Gupta *et al.* [13] was replaced by a full-text publication (Brixner *et al.* 2008 [22]), which concerned the same study although with slight methodological changes in data analysis. A study performed by Dickson and Plauschinat, 2008 [23], included data collected in the population of people between the ages of 18 and 99 years old, while another study by Dickson and Plauschinat, 2008 [21], which was included in the review by Gupta *et al.*, 2010

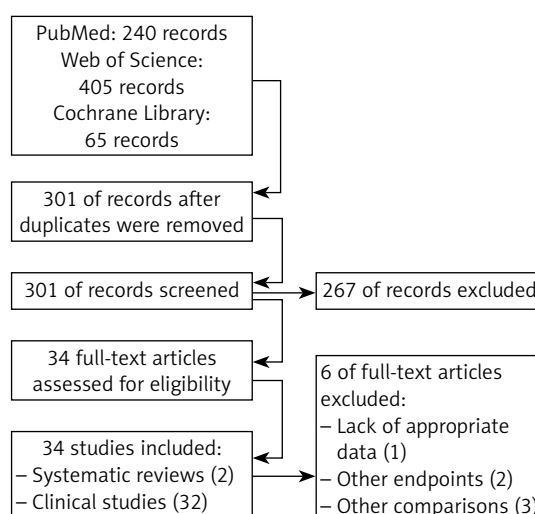


Figure 1. PRISMA flow diagram for selection of studies identified in the systematic review

[13], contained data collected in the population of people between the age of 65 and 99 years old (2 samples from the same study's population).

Six new retrospective studies were identified [27, 28, 40, 43–45], but only four met the criteria for inclusion in the analysis. Studies by Asplund *et al.* 1984 [17], Kumagai *et al.* 2013 [44], and Ulusoy *et al.* 2012 [45] were not included in statistical pooling because the data reported did not allow for their use in the review or the clinical assessment was different in those studies.

Finally, in our analysis we included data from four studies [18–21], which were also taken into account by Gupta *et al.* and Sherrill *et al.*, from 5 studies [2–14, 17–26, 30–39] which were included only by Sherrill *et al.* and from 6 new identified studies [3, 27, 28, 43, 44].

Characteristics of the identified studies [17–28, 30–40, 43–45] are shown in Table I.

Adherence

In our analysis 11 retrospective cohort studies and 1 nonrandomized trial reporting data on adherence to medication in hypertensive patients were taken into account (studies providing information on the average MPR or PDC or the number of adherent patients in each group).

A meta-analysis of the 2 retrospective cohort studies that defined being adherent as having an MPR of 0.8 or higher demonstrated a significantly ($p < 0.001$) higher percentage of adherent patients on FDC treatment in comparison with those on FEC treatment (pooled OR at 1.47; 95% CI: 1.23–1.74). Similar results were obtained in a meta-analysis of the 2 retrospective cohort studies with the PDC as the measure of adherence, although with significant heterogeneity of effect sizes ($p < 0.001$). A significant increase in the rate of adherence on FDC treatment was also obtained in 1 prospective clinical trial ($p = 0.032$; Figure 2).

Nine retrospective cohort studies showed the results for the average MPR (4 studies reported variances and 4 did not have variances available) or PDC values (1 study). A meta-analysis of 4 cohort studies demonstrated that using the FDC instead of the FEC was associated with a significant increase in the average MPR by absolute 13.1% (95% CIs: 8.9–17.2%, $p < 0.001$). A significant increase in the average PDC was also reported by Ferrario *et al.* ($p < 0.001$; Figure 3) [28].

Persistence

Data concerning persistence were included in the 6 identified studies. One of them [37] was previously identified by Gupta *et al.* [13], and four [22, 24, 26, 37] were previously described by Sherrill *et al.* [12]. The sixth study was identified in our search. A study by Hasford *et al.* 2007, in-

cluded by Sherrill *et al.* [12], was excluded from the meta-analysis due to different definitions of FDC and FEC in the compared groups [39]. A meta-analysis performed only on the basis of retrospective cohort studies showed significantly higher persistence among patients treated with the FDC when compared with those treated with the FEC. After 6 and 12 months of treatment, the number of patients on FDC treatment was significantly higher than that of those on FEC treatment ($p = 0.024$ and $p = 0.012$, respectively; Figure 4). A significant increase in the duration of treatment was also identified ($p < 0.001$; Table II).

Efficacy in blood pressure lowering

Nine trials included in the systematic review by Gupta *et al.* [13] provided information on blood pressure-lowering efficacy, and additionally, three of those trials reported the influence on both systolic and diastolic blood pressures.

Apart from the studies found by Gupta [13] and described in his systematic review, we identified three additional clinical trials [43–45] referring to blood pressure-lowering efficacy that were included in the narrative review – we evaluated the new trials and established that they are not eligible to be included in the updated meta-analysis.

In a cohort study performed by Bronsert *et al.* [43], patients receiving FDC treatment in comparison with those receiving FEC treatment showed a significantly greater reduction in systolic blood pressure (–5.3 mm Hg; 95% CI: –6.5 to –4.1) and diastolic blood pressure (–4.1 mm Hg; 95% CI: –4.8 to –3.4). The analysis was adjusted for the difference in confounder variables between the compared groups. A significantly higher rate of blood pressure normalization on FDC treatment in comparison with FEC treatment was also found ($p < 0.001$) [43]. Kumagai *et al.* [44] found that home blood pressure obtained by treatment was significantly lower in patients receiving FDCs than those receiving FECs, and this was accompanied by increasing adherence to medication ($p < 0.01$). On the other hand, Ulusoy *et al.* [45] demonstrated a reduction in all-day, daytime, night-time, and early morning systolic and diastolic blood pressures (blood pressure variability) in the FEC group as compared with the FDC group. However, the conclusions should probably be attributed to the difference in the time of administration of FEC compounds in the control group (valsartan in the morning and amlodipine in the afternoon in the control group; FDC in the morning in the study group) [45].

Other health outcomes and adverse events

Unfortunately, as in the case above, we have not identified new data on adverse effects, which

Table I. Characteristics of primary studies included in the review

Study	Study design	Study group FDC	Control group FEC	n FDC/ n FEC (total N)	Follow-up period	Proportion of women (%)	Age [years]	Outcome included in review	Quality of research
Solomon and Dawes 1980 [30]	RCT, double-blind, parallel study	Bendroflumazide 2.5 mg + propranolol 80 mg	Bendroflumazide 2.5 mg, propranolol 80 mg	14/14 (20)	14 weeks	50/50	44 [28; 63]	Change in blood pressure, safety profile, compliance	Good
Nissinen and Tuomilehto 1980 [31]	RCT, double-blind, parallel study	Atenolol 100 mg + chlorthalidone 25 mg	Atenolol 100 mg, chlorthalidone 25 mg	23/23 (23)	16 weeks	62.2/34.8	47.9 [31.0; 62.0]	Change in blood pressure, safety profile	Good
Asplund <i>et al.</i> 1984 [17]	RCT, parallel study, multicenter	Pindolol 10 mg + clopamide 5 mg	Pindolol 10 mg, clopamide 5 mg	80/80 (160)	8 months	61.2/38.8	51	Change in blood pressure, safety profile, compliance	Fair
Olvera <i>et al.</i> 1991 [32]	RCT, parallel study	Lisinopril 20 mg + thiazide 12.5 mg	Lisinopril 20 mg, thiazide 12.5 mg	14/14 (29)	14 weeks	No data	[30; 70]	Change in blood pressure, safety profile	Fair
Mancia and Omboni 2004 [33]	RCT, parallel study, multicenter	Candesartan cilexetil 16 mg + HCTZ 12.5 mg	Candesartan cilexetil 16 mg, HCTZ 12.5 mg	195/203 (409)	12 weeks	64/36	55.5 [26.0; 79.0]	Change in blood pressure, blood pressure normalization (diastolic blood pressure < 90 mm Hg and/or systolic blood pressure < 140 mm Hg)	Good
Bengtsson <i>et al.</i> 1979 [34]	Non-RCT, crossover study	Oxprenolol 80 mg + chlorthalidone 10 mg	Diuretic, β -blocker	28/28 (34)	16 weeks	53.6/46.4	56.3 [33.0; 79.0]	Change in blood pressure	Fair
Ebbutt and Elsdon-Dew 1979 [35]	Non-RCT, crossover study, multicenter	Oxprenolol 160 mg + cyclopenthiazide 0.25 mg	Oxprenolol, cyclopenthiazide	30/30 (47)	12 months	36.7/63.3	59	Blood pressure < 160/95 mm Hg	Fair

Table I. Cont.

Study	Study design	Study group FDC	Control group FEC	n FDC/ n FEC (total N)	Follow-up period	Proportion of women (%)	Age [years]	Outcome included in review	Quality of research
Forrest 1980 [36]	Non-RCT, crossover study	Oxprenolol hydrochloride 160 mg + cyclopenthiiazide 0.25 mg	Diuretic, β-blocker	1050/1050 (1117)	8 weeks	34.7/65.3	56.5	Change in blood pressure, safety profile	Fair
Schweizer <i>et al.</i> 2007 [18]	Non-RCT, crossover study, multicenter	Valsartan 160 mg + HCTZ 25 mg	Candesartan 32 mg, HCTZ 25 mg	138/197 (197)	6 months	47.6/52.4	58.15 [22.0; 79.0]	Change in blood pressure, safety profile, compliance	Fair
Dezii 2000 [37]	Retrospective cohort study	Lisinopril + HCTZ	Lisinopril, diuretic	1644/624 (2268)	1 year	No data	No data	Persistence	Good
Dezii 2000 [37]	Retrospective cohort study	Enalapril maleate + HCTZ	Enalapril maleate, diuretic	969/705 (1674)	1 year	No data	No data	Persistence	Good
Taylor and Shohelber 2003 [19]	Retrospective cohort study	Amlodipine besylate + benazepril HCl	DHP CCB, ACEI	2754/2978 (5732)	2 years	50/50	53 [18; 64]	Compliance	Good
Gerbino and Shohelber 2007 [20]	Retrospective cohort study	Amlodipine besylate + benazepril HCl	DHP CCB, ACEI	2839/3367 (6206)	1 year	No data	No data	Adherence	Excellent
Jackson <i>et al.</i> 2006 [38]	Retrospective cohort study	Valsartan + HCTZ	Valsartan, HCTZ	8150/561 (8711)	1 year	No data	> 18	Persistence	Good
Hasford <i>et al.</i> 2007 [39]	Retrospective cohort study	ACEI + other	ARB	558/418 (976)	3 years	55.8/44.2	65	Persistence	Good
Dickson and Plauschinat 2008a [21]	Retrospective cohort study	Amlodipine besylate + benazepril HCl	DHP CCB, ACEI	2336/3368 (5704)	5 years	17.4/82.6	76	Compliance	Good
Brixner <i>et al.</i> 2008 [22]	Retrospective cohort study	Valsartan + HCTZ	Valsartan, HCTZ	8150/561 (8711), some results presented among random sample of 1628 FDC patients (2189)	1 year	52.7	≥ 18	Adherence, persistence	Good

Table I. Cont.

Study	Study design	Study group FDC	Control group FEC	n FDC/ n FEC (total N)	Follow-up period	Proportion of women (%)	Age [years] Outcome included in review	Quality of research
Dickson and Plauschinat 2008b [23]	Retrospective cohort study	Amlodipine + benazepril	DHP CCB, ACEI	3363/713 (4076)	1 year	74.7	Average 62.2 (range: 18–99) Adherence	Good
Hess <i>et al.</i> 2008 [24]	Retrospective cohort study	ARB + HCTZ, ACEI + HCTZ, ACEI + CCB	ARB, HCTZ; ACEI, HCTZ; ACEI, CCB	7224/7225 (14449)	1 year	56.9	Average 62.06 and 62.86 Adherence, persistence	Good
Shaya <i>et al.</i> 2009 [25]	Retrospective cohort study	ACEI + HCTZ or ACEI + CCB	ACEI, HCTZ or ACEI, CCB	202/366 (566)	1 year	63.73	≥ 18 Adherence	Fair
Yang <i>et al.</i> 2010 [26]	Retrospective cohort study	ARB + CCB, ARB + HCTZ, or ACEI + HCTZ	ARB, CCB; ARB, HCTZ; or ACEI, HCTZ	382476/197375 (579851)	6 months	53.6	Average 56.8 and 63.1 (≥ 18) Adherence, persistence	Good
Zeng <i>et al.</i> 2010 [27]	Retrospective cohort study	ARB + CCB	ARB, CCB	2213/2312 (4525)	13 months	47.3–60.6	Average 60.12 and 67.39 (≥ 18) Adherence, persistence	Fair
Ferraro <i>et al.</i> 2013 [28]	Retrospective cohort study	Amlodipine + olmesartan	Amlodipine, ARB	4864/7748 (12612)	12 months	45.6	Average 53.8 and 60.7 (≥ 18) Adherence, persistence, rate of cardiovascular events	Good
Bronsert <i>et al.</i> 2013 (FDC vs. FEC only) [43]	Retrospective cohort study	All available FDCs	All available FECs	795/712 (1507)	6 months	54.5	52.9–61.9 Change in blood pressure	Fairly
Kumagai <i>et al.</i> 2013 [44]	Prospective observational study, nonrandomized	ARB + amlodipine	ARB, amlodipine	136/60 (196)	3 months	43.0	Average 69 Change in blood pressure	Good
Ulusoy <i>et al.</i> 2012 [45]	Prospective observational study, nonrandomized	Valsartan + amlodipine	Valsartan and amlodipine within 12-hour interval	43/42 (85)	–	67.1	Average 59.2 and 55.8 Blood pressure variability	Good
Jackson <i>et al.</i> 2008 [40]	Retrospective cohort study	Valsartan + HCTZ, amlodipine	Valsartan, HCTZ, amlodipine	619/65 (684)	12 months	58.2	≥ 18 Adherence	Fair

CCB – calcium channel blocker, ACEI – angiotensin-converting enzyme inhibitor, HCTZ – hydrochlorothiazide, DHP – dihydropyridine, ARB – angiotensin II receptor blockers.

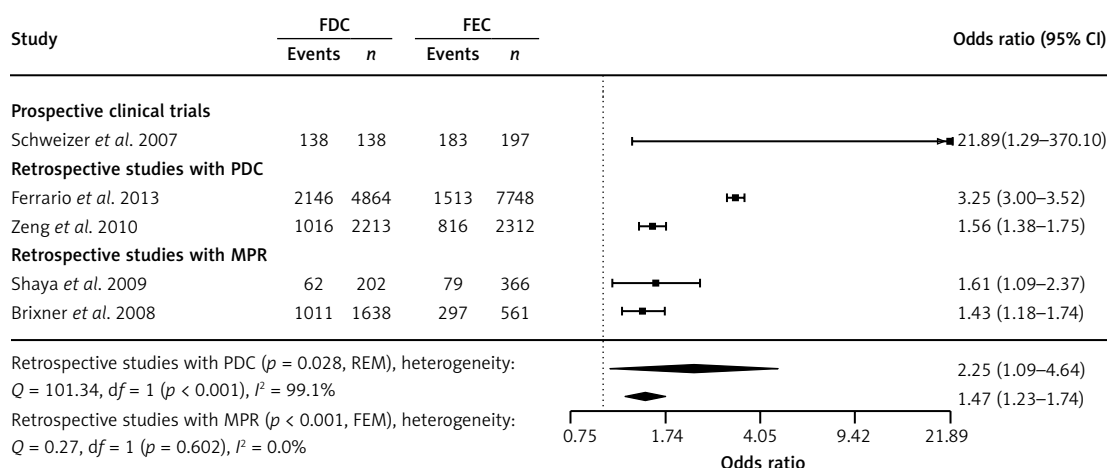


Figure 2. Meta-analysis of odds ratio for adherence to treatment. Events represent the number of patients meeting the definition of adherence (MPR or PDC ≥ 0.8). Odds ratio (OR) presented for FDC in comparison with FEC, with 95% confidence intervals (CI)

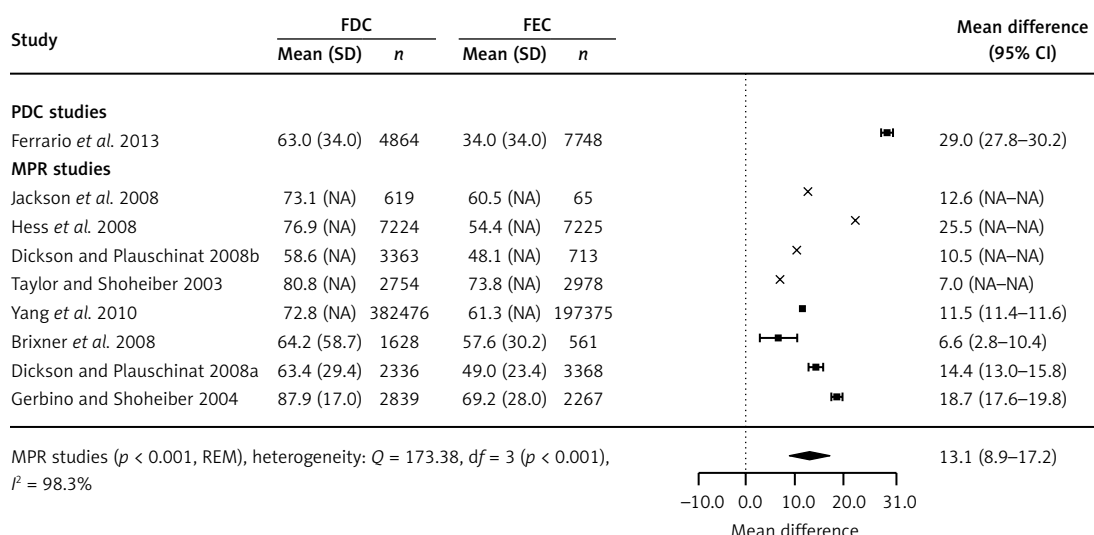


Figure 3. Meta-analysis of weighted mean difference in MPR or PDC. Mean difference presented for FDC in comparison with FEC, with 95% confidence intervals (CI). Studies not reporting variance for outcomes marked by cross estimates

NA – not available.

could be incorporated into the meta-analysis. However, Ferrario *et al.* 2013 [28] reported the results regarding the prevalence of cardiovascular events. The analysis of this retrospective cohort study demonstrated that a significantly lower number of patients on FDC treatment experienced cardiovascular events compared with patients on FEC treatment (OR = 0.31; 95% CI: 0.24–0.39).

Bias assessment and heterogeneity

Significant heterogeneity was observed in relation to all of the endpoints included in the review when all studies were pooled (data not shown). Subgroup analyses reduced the heterogeneity for some outcomes (odds for being adherent to treatment as measured with MPR in cohort stud-

ies, differences in average MPR between cohort studies), while for others heterogeneity remained significant.

A series of univariate and multivariate meta-regression analyses for 2 endpoints was carried out (adherence rates and average measure of adherence; 12 studies). The following predictors were taken into account: type of the study (prospective vs. retrospective), measure of adherence (PDC vs. MPR), duration of follow-up, percentage of women, and mean age of study participants. Based on the results obtained from meta-regression analyses, there was no significant effect of any of the predictors (data not shown).

The publication bias was not identified, although a reliable conclusion cannot be drawn

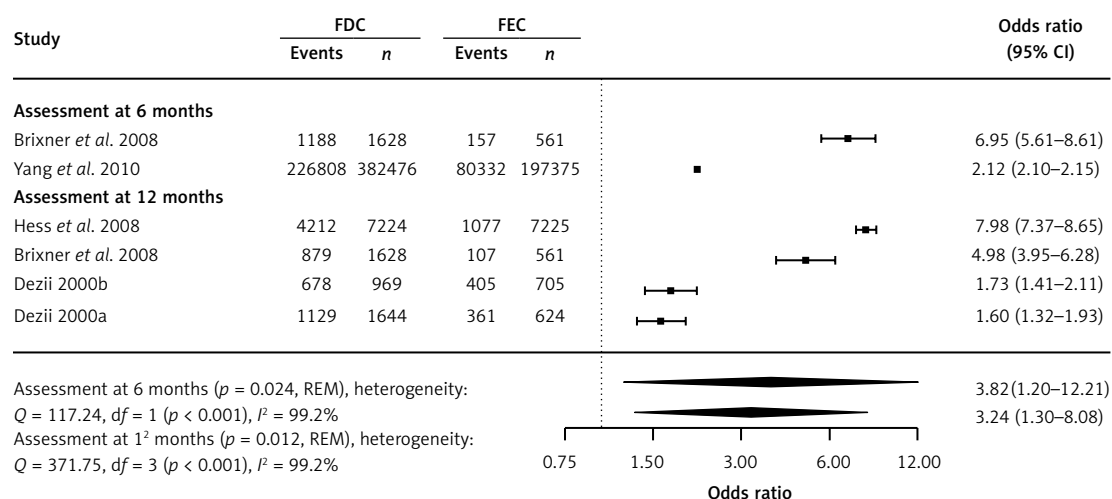


Figure 4. Meta-analysis of persistence. Events represent the number of patients meeting the definition of persistence. Odds ratio (OR) presented for FDC in comparison with FEC, with 95% confidence intervals (CI)

Table II. Clinical efficacy (continuous endpoints) of fixed-dose combinations (FDC) compared with free-equivalent combinations (FECs): persistence defined as average duration of treatment

Study	FDC group Mean \pm SD (N)	FEC group Mean \pm SD (N)	Effect size (95% CI)	P-value
Zeng <i>et al.</i> 2010 [35]	215.56 \pm NA (2213)	174.48 \pm NA (2312)	HR = 0.66 (0.63–0.70)	< 0.001
Ferrario <i>et al.</i> 2013 [36]	339.76 \pm 224.08 (2146)	233.72 \pm 238.56 (1513)	MD = 106.04 (90.90–121.18)	< 0.001

HR – hazard ratio, MD – mean difference, NA – not available.

owing to the small number of studies. Neither the funnel plots nor Egger's test indicated any association between the effect size and study size.

Discussion

A systematic review with a meta-analysis and narrative synthesis was conducted to compare the effectiveness of the FDC and FEC with regards to adherence (compliance) to medication, persistence to medication, and other clinically important endpoints during treatment of arterial hypertension. The results of the comparison can be important for the choice of treatment because the majority of patients with hypertension need more than 1 drug to control blood pressure.

Based on the synthesis of direct-comparison studies, it was found that FDC treatment is associated with a significant improvement in adherence and persistence in comparison with FEC treatment. It can be argued that the increase in adherence and persistence to FDC treatment in comparison with FEC treatment should result in a greater reduction in blood pressure and thus in obtaining lower blood pressure values. We did not identify any clear evidence to confirm this effect. The evidence for the benefit of FDCs over FECs

regarding the blood pressure-lowering effect was sparse and indicated only in large cohort studies. However, we found direct evidence for the reduction in the rate of cardiovascular events on FDC treatment.

The reduction in the rate of cardiovascular events can be indirectly confirmed by the results of 2 studies indicating that patients adherent to antihypertensive treatment are experiencing minor cardiovascular events. In a study that included patients with hypertension and without cardiovascular disease at baseline, a reduction in the annual risk of cardiovascular events by 22% (95% CI: 13–30%) was observed among adherent compared with nonadherent patients [46]. Similarly, a study that included patients with hypertension and without prior stroke reported a reduction in the risk of stroke and death by 8% (95% CI: 4–13%) and 7% (95% CI: 4–10%), respectively, among adherent versus nonadherent patients [47].

In general, our results are in line with the previously published systematic reviews by Sherrill *et al.* 2011 [12] and Gupta *et al.* 2010 [13], although some changes were observed, especially when comparing the conclusions with the latter study.

Sherrill *et al.* 2011 [12] demonstrated significantly higher adherence to treatment in the FDC group compared with the FEC group, based on a meta-analysis of studies reporting average MPR in the groups (13.31%, 95% CI: 8.26–18.35%).

Likewise, Gupta *et al.* [13] revealed that the adherence ratio in the FDC group was 1.2 times higher than that in the FEC group. However, they found that an increase in adherence was not statistically significant according to the pooled results of prospective trials, had borderline significance according to the pooled results of cohort studies, and was statistically significant according to the pooled results of all studies – prospective and retrospective combined [13].

Similarly, Bangalore *et al.* 2007 [48] found that FDC treatment decreased the risk of medication noncompliance in patients with hypertension, tuberculosis, diabetes, and human immunodeficiency virus.

Considering patient's persistence measured by the prescription refill interval and as duration of treatment, a significant advantage of FDC over FEC was identified. This is in line with the results reported by Sherrill *et al.* 2011 [12] (pooled risk ratio for 5 studies at 2.13; 95% CI: 1.11–4.09), but not with those reported by Gupta *et al.*, 2010 [13], who found no statistically significant differences between the FDC and FEC groups (pooled OR for 3 studies at 1.54; 95% CI: 0.95–2.49). These discrepancies might have been caused by the inclusion of a greater number of studies in our analysis compared with the analysis by Gupta *et al.* [13], the replacement of data from the conference abstract (Jackson *et al.* 2006 [38]) by the full-text publication (Brixner *et al.* 2008 [22]), or by the bias in data extraction or analysis (effect size estimation and description) in the meta-analysis previously published by Gupta *et al.* [13]. Interestingly, Hasford *et al.* 2007 demonstrated that persistence was the longest for FDCs of angiotensin receptor blockers than for FDCs of other drug classes. After 3 years of follow-up, 17.7% of the patients in the FDC group and only 3.2% of those in the FEC group were still on the initial treatment, although differences in active substances used in both arms were identified [39].

The meta-analysis by Gupta *et al.* showed a nonsignificant decline in the rates of adverse effects associated with the use of the FDC as compared with the use of the FEC (OR = 0.80; 95% CI: 0.58–1.11) [13]. We have found no new evidence on the safety profile, so the results presented by Gupta *et al.* 2010 [13] seem to be currently valid, and therefore we did not perform a meta-analysis regarding this endpoint. Only 1 retrospective study provided evidence concerning the incidence of cardiovascular events in the compared groups. The results for blood pressure and cardiovascular

events should be interpreted with caution owing to the absence of other studies reporting data on these outcomes. We relied on the results of retrospective nonrandomized studies, which by definition have less credibility than prospective randomized clinical trials. On the other hand, reliable randomized clinical trials will be difficult to conduct for adherence-based therapies.

As for the reduction in systolic and diastolic blood pressures and normalization of blood pressure, no new study that could expand the meta-analysis by Gupta *et al.* 2010 [13] was identified. Instead, 2 large retrospective cohort studies by Bronsert *et al.*, 2013 [43], and Kumagai *et al.*, 2013 [44], were found. Both studies indicated that blood pressure was significantly lower in patients receiving FDC treatment than in those receiving FEC treatment. However it should be noted that Gupta *et al.* [13] found a higher but not statistically significant ($p > 0.05$) difference between the FDC and FEC in the reduction of both systolic and diastolic arterial blood pressures (–4.1 mm Hg; 95% CI: –9.8 to 1.5 and –3.1 mm Hg; 95% CI: –7.1 to 0.9, respectively). The probability of normalization of blood pressure was also comparable ($p > 0.05$) in both groups [13].

Although some contradictory conclusions were obtained by Ulusoy *et al.* [45] (lower blood pressure variability during FEC treatment than during FDC treatment, which could result in a reduced rate of cardiovascular events), the finding on the advantage of FDC over FEC regarding cardiovascular events diminished the significance of that effect.

In general, the major limitation of our review is the fact that the conclusions were mainly based on the results of retrospective cohort studies owing to the lack of adequate randomized trials. Moreover, the studies were characterized by high heterogeneity in terms of methodology and clinical approach. The absence of conformity for possible disturbing factors in the event of some observational studies and nonrandomized trials in our meta-analysis is another limitation. Similarly, the included studies did not take into account the presence of comorbidities and concomitant therapies. All these limitations may have affected our results. However, we did not aggregate results of studies with significant differences in design and outcomes, thus providing reliable estimates of effect sizes.

In conclusion, this systematic review besides updating the previous results for comparison of the effectiveness of FDCs and FECs in hypertensive patients also provides more accurate results through the use of a separate meta-analysis stratified in view of the definition of outcomes related to adherence or period of observation in case of persistence and additionally assessments of the

impact of FDCs on incidence of cardiovascular events.

Our analysis demonstrated that administration of the FDC for antihypertensive treatment is associated with a statistically significant improvement in the cooperation between a doctor and a patient in comparison with FECs (increased adherence and persistence to the treatment schedule). It was shown that the use of FDCs of hypertensive agents may have a positive effect on blood pressure and is associated with a lower risk of cardiovascular events compared with the use of FECs, although clear evidence was sparse.

Well-designed randomized trials are needed to confirm our findings and to present a direct quantitative link between an increase in adherence or persistence to medication and clinically relevant outcomes such as the rate of cardiovascular events.

The introduction of FDC drugs to the standard treatment of hypertension could improve the quality of life and even provide additional benefits such as a reduced risk of cardiovascular events due to elevated adherence and persistence to the treatment.

Conflict of interest

The authors declare no conflict of interest.

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